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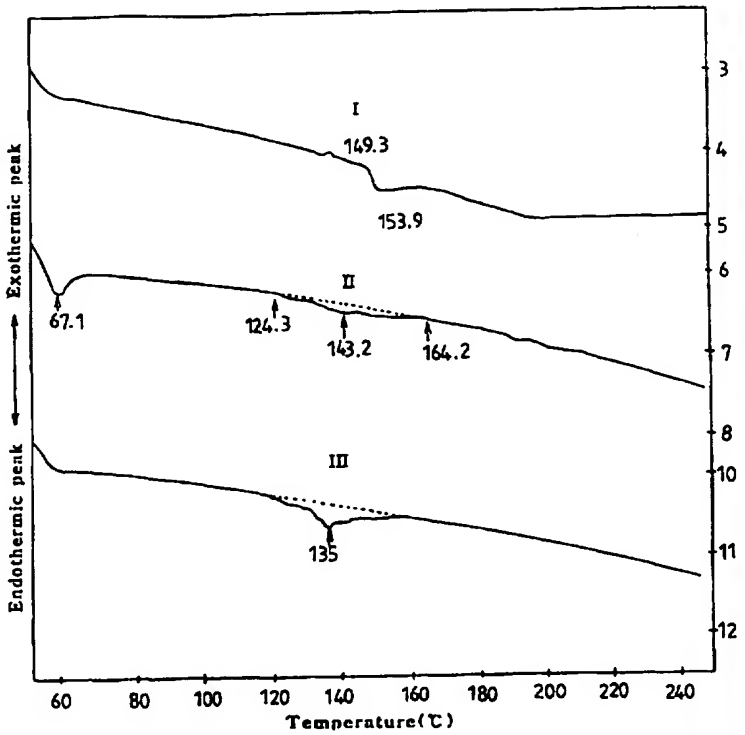
(54) Title: SOLID FORMULATIONS FOR ORAL ADMINISTRATION OF CYCLOSPORINE A

(57) Abstract

A novel solid micell dispersion imparting the remarkably improved bioavailability of cyclosporine A and oral solid formulations containing the same are disclosed. The solid micell dispersion of the present invention is prepared by conducting the following steps: (a) 5 to 10 ml of ethanol is mixed with 10 to 50 mg of cosolvent; (b) 100 mg of cyclosporine A is completely dissolved in the mixed solvents; (c) 70 to 200 mg of hydrophilic macromolecular matrix and 100 to 200 mg of surfactant are subsequently added to the solution; (d) once the dissolution of the added ingredients in the solution is completed, the solvent is evaporated under reduced pressure to yield the solids, and (e) the solids are dried to obtain the said solid micell dispersion.



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SOLID FORMULATIONS FOR ORAL ADMINISTRATION OF CYCLOSPORINE A

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a novel solid micell dispersion imparting the remarkably improved bioavailability of cyclosporine A, and oral solid dosage forms containing the same.

Description of the Prior Art

Cyclosporine A is a hydrophobic cyclic oligopeptide obtained from *Cylindrocarpon lucidum*, *Tolypocladium inflatum* and other fungi imperfecti [A. Ruegger *et al.*, *Helv. Chim. Acta* 59, 1075 (1976); M. Dreyfuss *et al.*, *J. Appl. Microbiol.* 3, 125 (1976)]. It has been well known to be a powerful immunosuppresant that appears to act mainly on T cells. It would be evaluated as an effective immunosuppresive drug in the following treatments: skin grafts, marrow transfer, cornea transfer or organ transfer such as heart, liver, kidney, pancreas, and the like. It has also been gradually applied for healing autoimmune diseases or inflammatory conditions (in particular, arthritis and rheumatoid diseases).

However, cyclosporine A ($C_{62}H_{111}N_{11}O_{12}$) has a relatively large molecular weight of 1,202.63 and is very hydrophobic. Due to such properties, cyclosporine A is slightly soluble in water (7.3 μg/ml at 37℃) [G. Ismailos et al., J. Pharm. Pharmcol., 43. 287-289, 1991] and

the bioavailability of cyclosporine A for oral administration is no more than 30% [K. Takada et al., Drug Delivery System 1, 1-7, 1986].

There are many references that show the improvements of cyclosporine A bioavailability. U.S Pat. No. 4,388,307 describes a solution in which the poor solubility of cyclosporine A is to be compensated by the use of Labrafil and olive oil as surfactant and solvent, respectively, along with the use of a large amount of ethanol. However, if such a solution is stored for an extended period, the content of ethanol in the solution is reduced by its evaporation and, thus, precipitates form. In addition, the solution has an unpleasant palatability. Moreover, the solution cannot be formulated into a solid dosage form.

Korean Patent Publication No. 90-4348 relates to cyclosporine microemulsion which consists of hydrophilic phase, hydrophobic phase and surface-active substances. The microemulsion is formulated into a soft capsule. However, the formulation of the microemulsion into a hard capsule is only possible using the Quali-Seal technique, and the formulation of the microemulsion into a tablet is impossible.

Korean Patent Publication No. 90-12625 teaches a method of preparing a solid dosage unit for oral administration of cyclosporine by dissolving cyclosporine and fatty acid saccharide monoester (e.g., saccharose monolaurate L-1695) in ethanol and then by evaporating the ethanol. However, this method is commercially disadvantageous because the fatty acid saccharide monoester is expensive, and, in a case where a solid dosage unit (one capsule or tablet) containing

100 mg of cyclosporine is prepared according to the procedures of this method, very large amounts of fatty acid sacchride monoester (ranging from approximately 924 mg to 1960 mg) are required. As such, it is impossible for patients to swallow a single dosage unit, and thereby it must be divided into multiple dosages.

Most commercial formulations available for oral administration of cyclosporine are commonly characterized by being mixed with a large amount of vegetable oil. Once such formulations have been orally administered to patients, cyclosporine in oil phase must be dissolved in gastric juice of aqueous phase in order to be absorbed into the gastrointestinal tract. However, the degree of dissolution of cyclosporine in gastric juice varies greatly in individual patients because it depends on the amount of bile juice secreted by the individual patient and the kinds and amount of food eaten by the patient, among other factors. Thus, it is best to minimize or completely exclude vegetable oil in the formulation of cyclosporine for oral administration.

Moreover, commercial formulations available for oral administration of cyclosporine have a common characteristic in containing a large amount of ethanol to dissolve cyclosporine. Although such ethanol keeps the cyclosporine dissolved in the formulations, once the formulations have been orally administered to a patient, the concentration of ethanol is diluted by gastric juice in the gastrointestinal tract, and the dissolution degree of cyclosporine falls rapidly. As such, the precipitates may form and may result in a significantly decreased absorption of cyclosporine. Thus, it is necessary to improve the absorption of cyclosporine without ethanol in the formulations.

Conventional methods to increase the dissolution or absorption of slightly soluble drugs include the solid dispersion method and the surfactant addition method (micell solution method). The solid dispersion method is to disperse slightly soluble drugs on hydrophilic macromolecular matrices, for example polyvinylpyrolidone, macromolecular polyethyleneglycol and Eudragit, so that the particle size of the drugs is reduced down to the molecular size of the drug. This method may be useful for the development of the solid formulations. However, once the solid dispersions, as prepared by such method, have been in water or gastric juice, the hydrophilic matrices are dissolved, and, immediately, the rapid dissolution of the drugs with molecular size proceeds until the phase gets temporarily supersaturated. Soon, equilibrium of the phase is no longer maintained, and the phase reaches saturation with the formation of the crystals of the drugs. According to the surfactant addition method, the mixture of slightly soluble drugs with surfactants has a disadvantage, in that, when it is administered in the form of solid formulations, the release of the drugs in the gastrointestinal tract is very slow.

There is much literature which supports the improvements on the bioavailability of slightly soluble drugs using either the aformentioned conventional solid dispersion method or surfactant addition method. However, no literature teaches the combination of both methods for the purpose of improving the bioavailability of slightly soluble drugs.

SUMMARY OF THE INVENTION

The present invention provide a novel solid micell dispersion suitable for oral administration of cyclosporine A, which comprises, based on 100 mg of cyclosporine A, 70 to 200 mg of hydrophilic macromolecular matrix, 100 to 200 mg of surfactant and 10 to 50 mg of cosolvent. In addition, the present invention provides the oral solid formulations containing the solid micell dispersion. The solid formulations of the present invention exhibit the remarkably superior bioavailability of cyclosporine A over currently commercial solid medicament preparations.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows analyses of the differential scanning calorimetry on cyclosporine A (I), a physically mixed composition of the ingredients of Example 9 (II), and a solid micell dispersion of Example 9 (III).

Figure 2 shows analyses of the differential scanning calorimetry on cyclosporine A (I), a physically mixed composition of the ingredients of Example 10 (II), and a solid micell dispersion of Example 10 (III).

Figure 3 shows analyses of the differential scanning calorimetry on a solid micell dispersion of Example 9 (I), as prepared by a solvent evaporation method, and a solid micell dispersion (II), as prepared by a fusion and solvent evaporation method using the same ingredients as Example 9.

Figure 4 shows a time-to-concentration profile of cyclosporine A in

whole blood after SD white male rats were orally adminstered with Sandimmun (●), formulations CyA-A(○) and CyA-B(▲) of Examples 13 and 14, respectively.

DETAILED DESCRIPTION OF THE INVENTION

It is now found that solid formulations containing the solid micell dispersion, as produced by the combination of the solid dispersion method and the surfactant addition method, resulted in the remarkably increased bioavailability of slightly soluble cyclosporine A.

A term "solid micell dispersion" herein is defined as the solid composition containing surfactants, which can dissolve slightly water-soluable drugs repidly and prevent the precipitation of drugs by forming micells in aqueous medium.

The solid micell dispersion, according to the present invention, are prepared by conducting the following steps:

(a) 5 to 10 ml of ethanol is mixed with 10 to 50 mg of cosolvent,

(b) 100 mg of cyclosporine A is completely dissolved in the mixed solvents,

(c) 70 to 200 mg of hydrophilic macromolecular matrix and 100 to 200 mg of surfactant are subsequently added to the solution,

(d) once the dissolution of the added ingredients in the solution is completed, the solvent is evaporated to yield the solids, and

(e) the solids are dried to obtain the said solid micell dispersion.

In the preferred aspects, the following may be used as the hydrophilic macromolecular matrix: PVP (polyvinylpyrolidone) K-30; PEG (polyethyleneglycol) 4000; PEG 6000; or a mixture of the two or more. The ratio of the composition may vary greatly, provided that PEG 6000 must be used in amounts of no more than 30 mg in order to avoid the precipitation of cyclosporine A. More preferred are, based on 100 mg of cyclosporine A, (i) a mixture of 50 mg of PVP K-30 and 50 mg of PEG 4000; (ii) a mixture of 5 to 10 mg of PVP K-30, 50 mg of PEG 4000 and 20 mg of PEG 6000 or (iii) a mixture of 50 mg of PVP K-30 and 10 to 20 mg of PEG 6000.

The preferred surfactant is Poloxamer 407 (Lutrol® F 127, block copolymer of polyoxyethylene and polyoxypropylene) or Poloxamer 188. The preferred amounts range from 100 mg to 200 mg based on 100 mg of cyclosporine A, and the more preferred amount is 150 mg.

The following may be used as cosolvent: glycerine, HCO-60, HCO-10, a mixture of HCO-60 and glycerine and a mixture of HCO-10 and glycerine. Preferred is a mixture of HCO-60 and glycerine. The most preferred cosolvent is a mixture of 20 mg of HCO-60 with 10 mg of glycerine. When glycerine is used in single, the amount must be between 20 mg and 50 mg because the deviation from the amount results in the poor dispersiblity or solidity of the solid micells. When HCO-10 is used in single, the amounts ranging from 30 mg to 50 mg result in the good dispersibility, solidity and solubility.

5 to 10 ml of ethanol may be used. Although these amounts of ethanol are used for producing the solid micell dispersion, according to the present invention, the finished solid micell

dispersion (following the final drying step) contains no ethanol.

There may be some disadvantages when the above conventional solvent evaporation method is applied in the production of the solid micell dispersion in bulk. First, the equipment for evaporating the solvents and drying the products are needed. Second, much energy is expended during the evaporating and drying processes. Third, as the solvents are evaporated, the "case hardening" effects take place. Thereby, the interior solvents in the semi-solid micells cannot move to the surface of the micells and, consequently, it is impossible to completely dry the micells.

Therefore, the inventors discovered a suitable method to produce the solid micell dispersion in bulk, in place of the solvent evaporation method. The inventors founded that, in the solvent evaporation method, when heating is conducted in order to accelerate the dissolution of the ingredients, the amount of ethanol can be decreased to approximately 1/80 of the amount currently used in the solvent evaporation method. In addition, once the heated solution is cooled to a room temperature, since the cool solution contains an appropriate amount of ethanol to sieve the solution, it is not necessary to evaporate the ethanol. After the cool solution is sieved through mesh 7 to mesh 10, the micells thus obtained are well dried at temperatures of 35 to 40℃ without the occurrence of the "case hardening" effects.

Accordingly, the present invention provides a process for producing, in bulk, the solid micell dispersion (hereinafter "fusion and solvent evaporation method"), which comprises the following steps:

(a) a solvent ethanol is mixed at 60℃ with cosolvent, cyclosporine A,

hydrophilic macromolecular matrix and surfactant to form the solution,

(b) the hot solution is cooled and sieved to obtain the solids, and

(c) the obtained solids are dried at temperatures of 35 to 40℃ to produce the desired solid micell dispersion.

The following may preferably be mentioned as solid formulations: tablets, pills, dragees, granules, powders, capsules and sachets. Such solid formulations are prepared by mixing the solid dispersing micells of the present invention with pharmaceutically acceptable carriers.

As carriers, diluent, lubricant (glidant) and disintegrant can be, for examples, used for further processing to give oral solid dosage forms of the present invention. The following may preferably be mentioned as the diluent: corn starch, lactose, spray-dried lactose and microcrystalline cellulose. The following may preferably be mentioned as the lubricant(glidant): talc, colloidal silicon dioxide (e.g., Aerosil 200). The following may preferably be mentioned as the disintegrant: carboxymethylcellulose, sodium starch glycolate (e.g., Primojel®), cross-linked polyvinylpyrolidone (e.g., Kollidon CL®), cross-linked carboxymethylcellulose sodium (e.g., Ac-Di-Sol®). The most preferred disintegrant is Kollidon CL® or the mixture of Kollidon CL® with Ac-Di-Sol®.

The following Examples illustrate solid micell dispersions of the present invention and a process for their production according to the solvent evaporation method or the fusion and solvent evaporation method.

Example 1

10 ml of ethanol was mixed with 20 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 10 mg of PEG 6000, 150 mg of PVP K-30 and 100 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 2

10 ml of ethanol was mixed with 20 mg of the combination of HCO-60 and glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 30 mg of PVP K-30 and 100 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 3

5 ml of ethanol was mixed with 20 mg of HCO-60 and 10 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 150 mg of PVP K-30 and 100 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 4

5 ml of ethanol was mixed with 20 mg of HCO-60 and 10 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 50 mg of PEG 4000, 100 mg of PVP K-30 and 100 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 5

5 ml of ethanol was mixed with 30 mg of HCO-60 and 20 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 10 mg of PEG 4000, 50 mg of PVP K-30 and 150 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 6

10 ml of ethanol was mixed with 30 mg of HCO-60. 100 mg of cyclosporine A was dissolved in the mixed solvents. 20 mg of PEG 4000, 50 mg of PVP K-30 and 150 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products.

The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 7

10 ml of ethanol was mixed with 30 mg of HCO-60. 100 mg of cyclosporine A was dissolved in the mixed solvents. 50 mg of PEG 4000, 20 mg of PEG 6000 and 150 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 8

10ml of ethanol was mixed with 20 mg of HCO-60 and 10 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 150 mg of PVP K-30 and 100 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 9

5ml of ethanol was mixed with 20 mg of HCO-60 and 10 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 50 mg of PEG 4000, 50 mg of PVP K-30 and 150 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the

solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 10

10 ml of ethanol was mixed with 20 mg of HCO-60 and 10 mg of glycerine. 100 mg of cyclosporine A was dissolved in the mixed solvents. 50 mg of PEG 4000, 20 mg of PEG 6000, 10 mg of PVP K-30 and 150 mg of Poloxamer 407 were subsequently added to the solution. After the complete dissolution, the solvents were evaporated at a temperature of 35℃ under reduced pressure using an evaporator to obtain the solid products. The obtained solid products were dried on a desiccator for 24 hours to produce the desired solid micell dispersion.

Example 11

5 g of glycerine and 10 g of HCO-60 were subsequently added to 50 g of ethanol. After the complete dissolution, 25 g of PVP K-30 was added to the solution. After the complete dissolution, 25 g of PEG 4000 was added to the solution which was in turn heated to 60℃ in order to complete the dissolution. 15 g of Poloxamer 407 and 50g of cyclosporine A, as previously sieved through mesh 30, were subsequently added to the solution. After the complete dissolution of cyclosporine A, 60 g of Poloxamer 407 was added to the solution which was in turn cooled to a room temperature with continuous stirring. The solution was sieved through mesh 7 to obtain the solids, and then the obtained solids were completely dried at a temperature of 40℃. The dried solids were sieved through mesh 20 to obtain the desired solid micell dispersion.

Example 12

5 g of glycerine was added to 50 g of ethanol. After the complete dissolution, 5 g of PVP K-30 was added to the solution. After the complete dissolution, 25 g of PEG 4000 and 10 g of PEG 6000 were subsequently added to the solution, which was in turn heated to 60℃ in order to complete the dissolution. 15 g of Poloxamer 407 and 50 g of cyclosporine, as previously sieved through mesh 30, were subsequently added to the solution. After the complete dissolution of cyclosporine A, 60 g of Floxamer 407 was added to the solution which was in turn cooled to a room temperature with continuous stirring. The solution was sieved through mesh 7 to obtain the solids, and then the obtained solids were completely dried at the temperature of 30℃. The dried solids were sieved through mesh 20 to the desired solid micell dispersion.

A analysis of the thermodynamic property of the solid micell dispersion of the present invention using the differential scanning calorimetry

All of the solid micell dispersion prepared by Examples 1 to 12 have sufficiently good solubility, dispersibility and solidity to produce solid formulations. The solid micell dispersion of Example 9 are superior over the others, in that 24 hours after the solid micells were dispersed in a distilled water, precipitates did not form. The solid micell dispersion of Example 10 are not as dispersible as those of Example 9, but they are comparable to the solid micell dispersion of Example 9 in terms of solubility and solidity.

As representative examples, the thermodynamic properties of the

solid micell dispersions of Examples 9 and 10 were analyzed by the differential scanning calorimetry. The following were analyzed as controls: (i) cyclosporine A; (ii) a physical mixture of the ingredients of Example 9; and (iii) a physical mixture of the ingredients of Example 10. Temperatures varied from 50℃ to 250℃ with the elevation rate of 20℃/min, and α-alumina was used as a reference. All samples were sieved through mesh 35, and 8 mg was applied to the DSC.

Figure 1 shows the endothermal peaks of cyclosporine A (I) in the vicinity of 150℃, physical mixture of Example 9 (II) in the vicinity of 60℃ and 130℃, and solid micell dispersion of Example 9 (III) in the vicinity of 135℃. Figure 2 shows the endothermal peaks of cyclosporine A (I) in the vicinity of 150℃, physical mixture of Example 10 (II) in the vicinity of 60℃ and 143℃, and solid micell dispersion of Example 10 (III) in the vicinity of 145℃.

The single endothermal peaks (III) shown in Figures 1 and 2 demonstrate that the solid micell dispersion of the present invention are homogeneous and have a decreased crystallinity.

In addition, the solid micell dispersion of Example 12, as prepared by the fusion and solvent evaporation method of the present invention, was also analyzed in the same manner as the aforementioned and was compared with the solid micell dispersion of Example 9. The results are shown in Figure 3. This shows that both micell dispersions are homogeneous and a decreased crystallinity.

Analysis of Particle Size by Dynamic Light Scattering Method

After a distilled water was added to each of solid micell dispersions of Examples 9 and 10, the size of the micell thus formed in solution was measured by the dynamic light scattering method. As reference, the contents of Sandimmun® were measured in the same manner. The results are shown in Table I below.

Table I

Formulation	Mean Size(nm)	Range(nm)
The solid micell dispersion of example 9	685.5	622 to 753
The solid micell dispersion of example 10	423.9	347 to 509
Sandimmun®	1798	1035 to 2599

The following Examples illustrate solid oral dosage forms and the process for their production according to the present invention.

Example 13

The following were mixed and pressed to give a tablet which weighs 200 mg and which contains 25 mg of cyclosporine:

Solid micell dispersion prepared by Example 11	95 mg
Corn starch	25 mg
Ac-Di-Sol®	25 mg
Kollidon CL®	25 mg
Talc	5 mg
Aerosil 200®	25 mg

Example 14

The following were mixed and pressed to give a tablet which weighs 200 mg and which contains 25 mg of cyclosporine:

Solid micell dispersion prepared by Example 12	90 mg
Corn starch	35 mg
Ac-Di-Sol®	25 mg
Kollidon CL®	25 mg
Talc	5 mg
Aerosil 200®	20 mg

Example 15

The following were mixed and filled into a capsule which contains 25mg of cyclosporine:

Solid micell dispersion prepared by Example 11	95 mg
Corn starch	35 mg
Aerosil 200®	5 mg
Magnesium stearate	2 mg

Example 16

The following were mixed and filled into a capsule which contains 25mg of cyclosporine:

Solid micell dispersion prepared by Example 12	90 mg
Corn starch	40 mg
Aerosil 200®	5 mg

Magnesium stearate	2 mg

Example 17

The tablet in Example 13 was film-coated using the following formula:

Hydroxypropylmethylcellulose	10 mg
Hydroxypropylcellulose-Low viscosity	0.1 mg
TiO_2	3.5 mg
Isopropyl alcohol	48 mg
Methylene chloride	120 mg

Example 18

The tablet in Example 14 was film-coated using the following formula:

Hydroxypropylmethylcellulose	10 mg
TiO_2	3.5 mg
PEG 6000-8000	2 mg
Methylene chloride	80 mg
Ethanol	80 mg

Pharmacodynamic Test

The solid formulations of Examples 13 and 14 were used as test samples and were designated as CyA-A and CyA-B, respectively. Sandimmun® (Lot No. 096 MFD 0393 EXP 0996) was used as a control.

For 12 hours prior to testing, SD male white rats were divided into three groups of five and were allowed to ingest only water with

abstinence from food. Each of CyA-A, CyA-B and control formulations were dissolved in 0.5 ml of aqueous solution. Each rat group was orally administered with the solution using a sonde. In the solution, each rat received a single dose equivalent to 10 mg of cyclosporine A per kg of body weight. At selected intervals (1, 2, 3, 4, 6, 10, 24 and 48 hours after administration), serial whole bloods were collected by 0.5ml each from the ocular capillary artery of each rat using a capillary tube pretreated with Heparin. The blood was then placed in a cap-tube pretreated with 25μl of 5% EDTA-2Na solution and they kept in cold storage at -20℃.

Blood samples were analyzed by a monoclonal fluorescence polarization immunoassay using TD_x® Cyclosporine Monoclonal Whole Blood reagent (Abbott Labs). 150μl of whole blood, 50μl of buffer containing 4% Triton-X100 surfactant, and 300μl of zinc sulfate solution (dissolved in a mixture of methanol and ethylene glycol) were blended in the test tube and then centrifuged at 9,500g for 5 minutes.

After proteins were completely precipitated, the whole supernatants were used to analyze the content of cyclosporine A using TDxFKx® ™(Abbott Labs). The monoclonal antibody fluorescein was used as a tracer of cyclosporine A. When the lot number of the reagents was changed, calibrators 0, 50, 100, 200, 500 and 1000 ng/ml were adjusted in order to keep the conditions of the appratus constant. In addition, the adjustment of the apparatus was performed bi-weekly in the same manner as above. Because the apparatus is able to measure cyclosporine A up to a limit of 1500ng/ml, in cases where the concentration of cyclosporine A in the samples exceeded 1500ng/ml, such samples were diluted and

again measured.

The test results were shown in Figure 4 and Table 5 below. From the data, it is evident that the solid formulations of the present invention are remakably superior to commercial solid formulations in terms of the bioavailability of cyclosporine A.

Table 5

Cyclosporine A concentrations in blood(ng/ml) (mean ± S.D. n=5)			
Time(hours)	Control	Formulations of the present invention	
	Sandimmun®	CyA-A	CyA-B
1	585.28 ± 192.33	1977.02 ± 326.25	1564.91 ± 425.86
2	928.03 ± 212.30	2113.78 ± 194.50	1768.38 ± 744.40
3	805.24 ± 131.60	2082.23 ± 196.85	1638.18 ± 611.36
4	743.40 ± 91.69	1686.99 ± 337.07	1421.48 ± 426.79
6	607.97 ± 107.09	1384.85 ± 304.97	1194.83 ± 178.81
10	408.43 ± 111.28	996.52 ± 229.92	799.13 ± 144.77
24	198.09 ± 89.68	275.62 ± 75.50	336.37 ± 117.47
48	48.76 ± 27.06	89.71 ± 24.30	119.08 ± 47.57

Pharmacokinetic parameters (mean ± S.D. n=5) of cyclosporine A following single oral administrations (10mg/kg) to 5 SD rats			
Parameters	Control	Formulations of the present invention	
	Sandimmun®	CyA-A	CyA-B
C_{max}(ng/ml)	959.43 ± 183.01	224.47 ± 110.09	1840.98 ± 657.01
T_{max}(hr)	2.20 ± 0.45	1.80 ± 0.84	2.00 ± 0.71
AUC_{48h}(ng · hr/ml)	12864.62 ± 2451.59	28097.36 ± 4811.10	25074.32 ± 6830.11
Relative BA_{48h}(%)	100%	218.4%	194.9%
AUC_{∞}(ng · hr/ml)	13804.93 ± 3112.19	29428.63 ± 5016.76	27280.23 ± 7548.98
Relative BA_{∞}(%)	100%	213.2%	197.6%
MRT_{48h}(hr)	12.51 ± 2.46	11.11 ± 0.63	12.60 ± 1.10
MRT_{∞}(hr)	15.85 ± 4.51	13.52 ± 1.11	17.33 ± 3.06
VRT_{48h}(hr^2)	124.56 ± 20.88	109.75 ± 8.73	135.06 ± 21.97

The maximum concentration (C_{max}) and the area under the curve (AUC) increased significantly for formulations of the present invention, and the time of peak blood level decreased. Mean residence times were not significantly different among them. The relative bioavailabilities of cyclosporine A from formulations of the present invention were almost twice as high as Sandimmun®.

WHAT IS CLAIMED IS:

1. A solid micell dispersion suitable for oral solid formulations of cyclosporine A, prepared by conducting the following steps:
(a) 5 to 10 ml of ethanol is mixed with 10 to 50 mg of cosolvent,
(b) 100 mg of cyclosporine A is dissolved in the mixed solvents,
(c) 70 to 200 mg of hydrophilic macromolecular matrix and 100 to 200 mg of surfactant are subsequently added to the solution,
(d) once the dissolution of the added ingredients in the solution is completed, the solvent is evaporated to yield the solids, and
(e) the solids are dried to produce the said solid micell dispersion.

2. The solid micell dispersion according to claim 1 wherein the said hydrophilic matrix comprises PVP K-30, PEG 4000 or PEG 6000, or a mixture of the two or more, the said surfactant comprises Poloxamer 407 or Poloxamer 188, and the said cosolvent comprises a mixture of HCO-60 and glycerine.

3. A solid formulation for oral administration of cyclosporine A comprising the solid micell dispersion of claim 1 and pharmaceutically acceptable carrier.

4. The solid formulation according to claim 3 wherein the said carrier comprises (i) diluent selected from a group consisting of carboxymethylcellulose, sodium starch glycolate, cross-linked polyvinylpyrolidone and cross-linked carboxymethylcellulose sodium or a mixture thereof, (ii) disintegrant selected from Kollidon CL® or a mixture of Kollidon CL® with Ac-Di-Sol® and (iii) lubricant

selected from talc or colloidal silicon dioxide.

5. A process for producing, in bulk, a solid micell dispersion suitable for oral solid formulations of cyclosporine A, which comprises conducting the following steps:

(a) a solvent ethanol is mixed at 60℃ with cosolvent, cyclosporine A, hydrophilic macromolecular matrix and surfactant to form the solution,

(b) the hot solution is cooled and sieved to obtain the solids, and

(c) the obtained solids are dried at temperatures of 35 to 40℃ to produce the said solid micell dispersion.

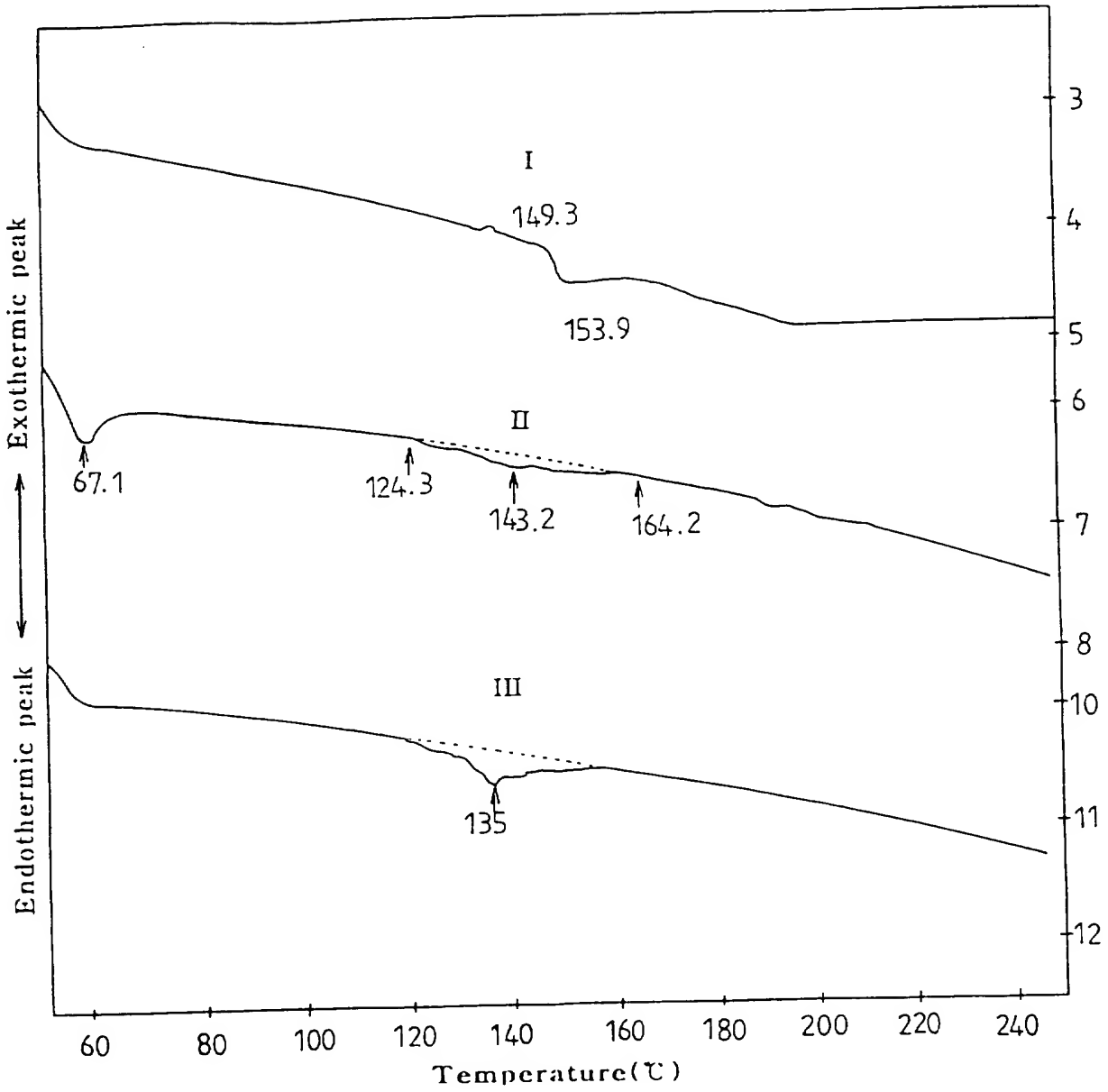
Exothermic peak
Endothermic peak
I
149.3
153.9
II
67.1
124.3
143.2
164.2
III
135
3
4
5
6
7
8
10
11
12
60
80
100
120
140
160
180
200
220
240
Temperature(℃)

Figure 1

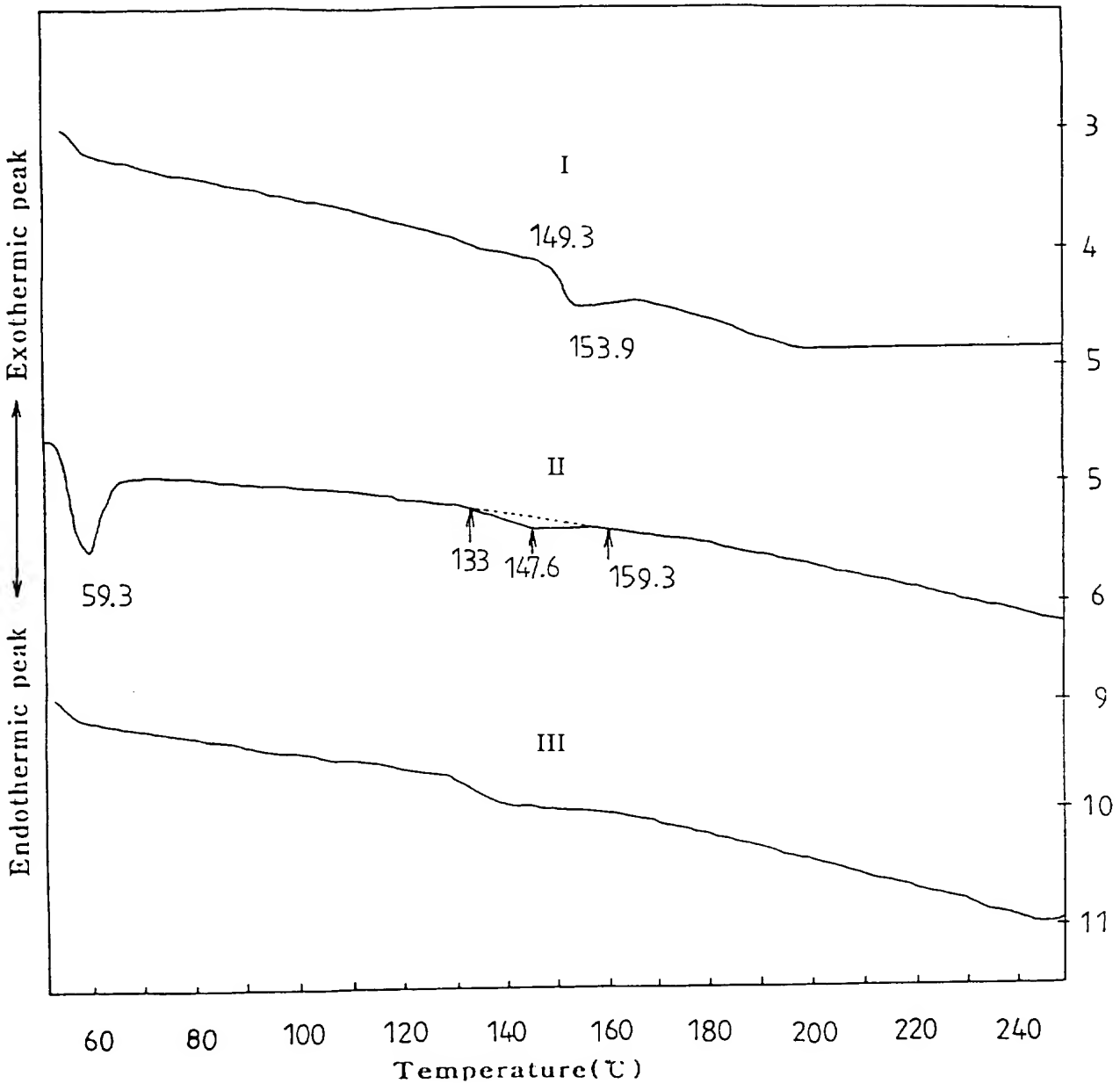
Exothermic peak
Endothermic peak
I
149.3
153.9
II
59.3
133
147.6
159.3
III
3
4
5
5
6
9
10
11
60
80
100
120
140
160
180
200
220
240
Temperature(℃)

Figure 2

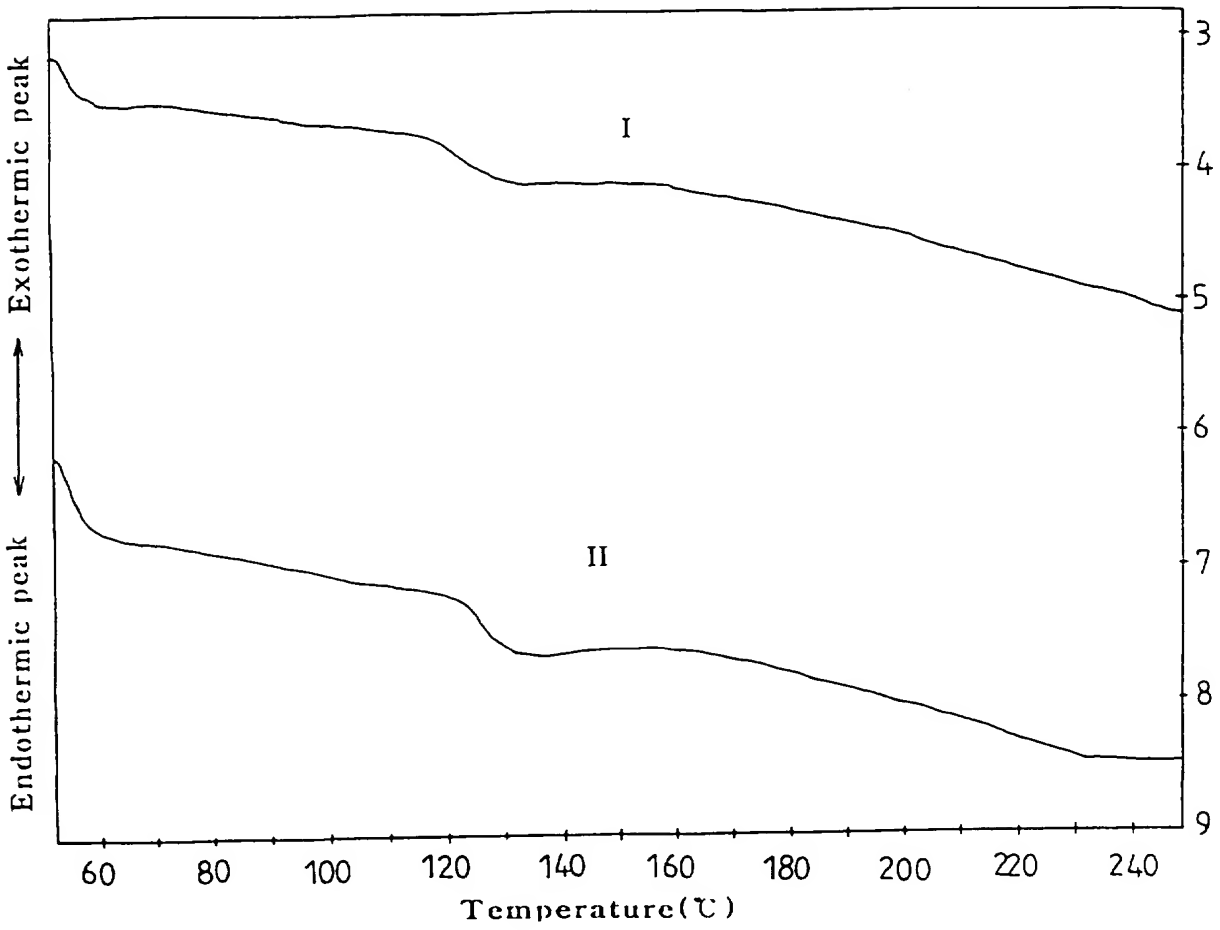
Exothermic peak
Endothermic peak
I
II
3
4
5
6
7
8
9
60
80
100
120
140
160
180
200
220
240
Temperature(℃)

Figure 3

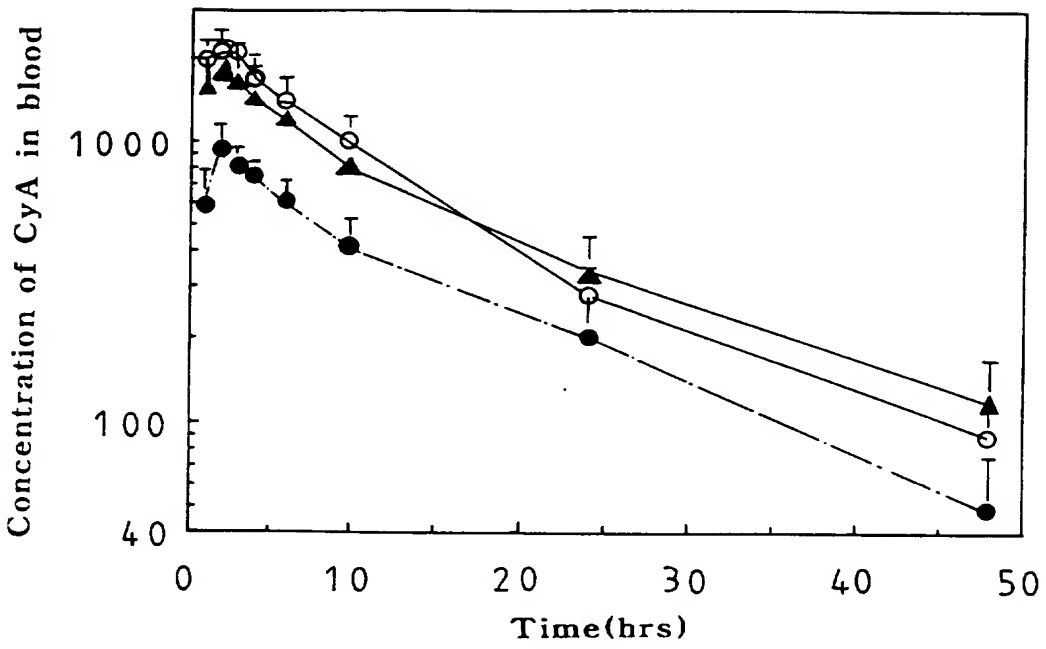
Concentration of CyA in blood
1000
100
40
0
10
20
30
40
50
Time(hrs)

Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 96/00008

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 61 K 38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 61 K 38/13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 388 307 A (CAVANAK) 14 June 1993 (14.06.83), claims 1,2.	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 April 1996 (02.04.96)	03 May 1996 (03.05.96)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Wolf
Facsimile No. 1/53424/535	Telephone No. 1/53424/133

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 96/00008

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		DE C3 2907460	06-05-97
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		IE B [illegible]	05-09-[illegible]
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